

REMARKS

Interview Summary

Applicants thank the Examiner and his supervisor, Examiner James Ketters, for participating in a telephonic interview with their undersigned attorney and his colleague, Mr. James Nolan, on 9 September 2003.

Amendments

Upon entry of the above amendments, claims 21 and 24-26 will be pending, with non-elected claims 1-20, 22, and 23 having been canceled. Per the examiner's suggestion in the Final Action, Applicants have added new claim 26, which represents claim 25 written in independent form. These amendments do not require a new search, nor do they raise new issues for consideration. Moreover, this amendment adds no new matter and is fully supported by the specification and claims as originally filed. Accordingly, it is submitted that this amendment places all currently pending claims (i.e., claims 21 and 24-26) in condition for allowance or in better condition for appeal. Therefore, entry of this amendment at this stage is proper.

Request for Reconsideration

Applicants respectfully request reconsideration in view of the following remarks. They also wish to highlight that responsibility for this application has been transferred to the undersigned, the prior powers having been recently revoked (see copy of attached postcard indicating the PTO's receipt of a new power of attorney on 17 June 2003).

Requirement For New Oath/Declaration

The Final Action provides that a new Declaration is required. Applicants wish to apologize for the confusion apparently caused by the reference in their prior response to the submission of a revised declaration, when in fact no such declaration was then filed. That said, Applicants respectfully draw the Examiner's attention to the first page of the declaration submitted as part of this application's initial filing. There, they clearly indicate that this

application claims priority to USSN 09/453,610, filed 3 DEC 1999. Moreover, among the documents submitted at the time this application was originally filed was a document amending the first paragraph of the specification to include a chain of priority. Entry of this amendment was reflected in the official filing receipt. For these reasons, Applicants respectfully submit that a new declaration is not necessary, and they request that the requirement for submission of a new declaration be withdrawn.

Formal Drawings

Applicants thank the Examiner for the approval of the formal drawings submitted 14 January 2003.

Rejection Under 35 U.S.C. § 112

Applicants thank the Examiner for withdrawing the § 112, 2nd paragraph, rejection.

Rejection Under 35 U.S.C. § 102

Applicants thank the Examiner for withdrawing the § 102 rejection.

Rejection Under 35 U.S.C. 103

Claims 21 and 24 again stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Strauss and Jaensich in view of Chernomordik, *et al.* Applicants respectfully traverse.

To establish a *prima facie* case of obviousness based on a combination of cited articles, three criteria must be met. First, there must be some suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine the articles' teachings. Second, there must be a reasonable expectation of success. Finally, the articles, when combined, must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not be based on Applicants' disclosure. See MPEP 706.02(j).

As discussed during the recent telephonic interview, Applicants respectfully submit that cited combination does not satisfy even one of these essential criteria. With regard to the

motivation to combine, Applicants note the absence of a logical connection between the two articles. The Strauss and Jaenisch paper presents one example of a proposed complementation strategy for assessing gene function. In their example, a gel-purified 150 kb YAC DNA containing an alpha-1(I) collagen transgene from Mus spretus was reportedly stably integrated into the Mus musculus genome using what was shown to be an extremely low efficiency micelle-mediated transfection protocol, where the micelles were formed using DOTMA. No teaching or suggestion was provided with regard to the use of any other micelle-forming material.

In contrast, the paper by Chernomordik, et al. reportedly addressed the influence of electric fields on the interaction of large, unilamellar, dye-containing liposomes with animal cells. There, three different lipids were reportedly mixed in a 1:1:1 ratio to make the liposomes used in the study. The three lipids were phosphatidylcholine from egg yolk, phosphatidylserine from bovine brain, and cholesterol. Nowhere does the Chernomordik, et al. paper teach or suggest that (i) DOTMA, or any other lipid composition, could be substituted for the three-lipid composition disclosed therein or (ii) the liposomes disclosed therein could be used to deliver nucleic acids, let alone chromosomes, to cells. Accordingly, neither of the cited papers provides anything to suggest their combination.

Moreover, the Chernomordik, et al. paper reported an increase in liposome binding on cell surfaces, but not necessarily internalization, after application of a short duration electric pulse. Specifically, those authors reported that the increase in liposome/cell binding did not happen at the moment of electric field application; instead, it reportedly took about 30 min. to develop tight binding. Significantly, they reported that their results could not be explained by "the translocation of liposomes via electropores in cell membranes" because "it is difficult to imagine the membrane of a viable cell developing pores with diameter(sic) more than 0.1 um ... and lifetime of the order of minutes". The Chernomordik, et al. paper, page 197, left column.

Put another way, the authors of the Chernomordik, et al. paper concluded that their observed effect was due to binding of intact liposomes to cell membranes, without subsequent internalization. They went on to postulate that the time-delayed electrostimulated increase in dye-containing liposome binding may have been related to changes in membrane organization.

In contrast to comments made in the Final Action, as Chernomordik, et al. discussed, internalization of liposomes does not necessarily follow liposome binding. Indeed, the reported results for Molt 4 cells led Chernomordik, et al. to conclude that even though their liposomes bound to the membranes of Molt 4 cells, they were not internalized.

This result (i.e., liposome binding to cell membranes without later internalization), and Chernomordik, et al.'s discussion of it, cannot fairly be said to provide a motivation to use electric fields to introduce DNA into cells using liposomes. Indeed, if anything, it teaches away from such an application, thereby undercutting not only the "motivation to combine" criterion, but also the "reasonable expectation of success" criterion.

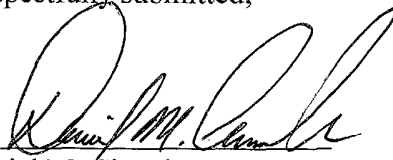
Applicants respectfully submit that a fair reading of the cited references reveals that they do not, in fact, teach or suggest each and every element of their claimed invention, as nothing in either of these references would lead one of ordinary skill in the art to reasonably expect that a method of substantially simultaneously contacting a cell and a liposome-encapsulated chromosome using an electric pulse would successfully transform the cell with the chromosome. For this reason, Applicants request withdrawal of the instant rejection.

CONCLUSION

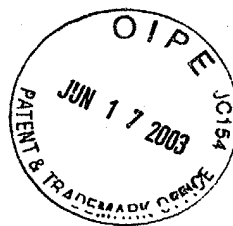
Applicants respectfully submit that all pending claims are in condition for allowance, and they earnestly solicit a notice to such effect. Should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at 858.735.7090 so that they may be promptly resolved.

Dated: 18 SEPT 2003

Respectfully submitted,

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To: Commissioner of Patents:
Re: Application number: 09/974,882
Attorney docket number: GTI-1320-CON1



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